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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,488	02/16/2000	MAURICE MOLONEY	9369-98	6010

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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1652	18

DATE MAILED: 12/04/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/402,488	MOLONEY ET AL.	
	Examin r	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *31-40 and 45-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30 and 41-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Claims 1-47 are pending in the application.

Applicants' amendment to the specification and claims 1, 5, and 27 in Paper No. 17, filed 09/18/01 is acknowledged.

Claims 1-30 and 41-44 are being examined on the merits.

Claims 31-40 and 45-47 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 14.

Applicants' arguments filed in Paper No. 17, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Due to the numerous amendments to the claims, the examiner requests that applicants provide a copy of all pending claims in subsequent communications.

Drawings

1. As stated in a previous Office action, the drawings submitted with this application have not been reviewed by a draftsperson at this time. Upon allowance of the application, the draftsperson will perform a review. Direct any inquiries concerning drawing review to the Drawing Review Branch (703) 305-8404.

Claim Objections

2. Claim 1 is objected to because of the following informalities: the term "transforming a host cell an expression vector" is grammatically incorrect and should be replaced with, for example, "transforming a host cell with an expression vector". Appropriate correction is required.

3. Claim 27 is objected to because of the use of the terms "SEQ.ID.NO 1" and "SEQ.ID.NO. 3". It is suggested that the terms be replaced with proper sequence identifiers such as "SEQ ID NO:1" and "SEQ ID NO:3", respectively.

Claim Rejections - 35 USC § 112, Second Paragraph

4. Claims 1-30 and 41-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claims 1 (claims 2-19 dependent therefrom), 20 (claims 21-30 dependent therefrom), 41 (claims 43 and 44 dependent therefrom), and 42 are indefinite in the recitation of "a nucleic acid sequence encoding a pro-peptide derived from an autocatalytically maturing zymogen". The claims are indefinite because it is unclear as to whether said nucleic acid encodes only a pro-peptide or further encodes the mature form of the zymogen. Based on the limitations provided in claims 6, 25, and 44, it appears that the chimeric nucleic acid sequence of claims 1, 2, 41 and 42 encodes the pro-peptide linked to a mature form of the zymogen, i.e., the zymogenic form of the protease. It is suggested that applicants clarify the meaning of the claims.

6. Claims 1 (claims 4-19 dependent therefrom), 2, 3, 21-23, 41 (claims 43 and 44 dependent therefrom), and 42 are indefinite in the recitation of "derived from". It is unclear whether the term "derived from" is meant to be interpreted as a pro-peptide that is a part of or isolated from an autocatalytically maturing zymogen or alternatively, is meant to be interpreted as a mutant form of a pro-peptide from an autocatalytically maturing zymogen. It is suggested that applicants clarify the meaning of the term by, for example, replacing the term "derived from" with "from".

7. Claim 4 is indefinite in the recitation of "group comprising". It is suggested that applicants replace the term with, for example, "group consisting of".

8. Claims 10, 11 (claim 12 dependent therefrom), 16, and 17 (claim 18 dependent therefrom) are confusing in the recitation of "in vivo conditions". Example 3 at page 17 of the instant specification

describes "in vivo" partial cleavage of the pro-peptide using a red turnip beetle gut extract. A typical definition of "in vivo" is provided in "Dorland's Illustrated Medical Dictionary ((29th Edition (2000), W. B. Saunders Company, Philadelphia, PA)) as "within the living body". Therefore, one of skill in the art would not consider such conditions to be "in vivo" and would instead consider said conditions "in vitro". It is suggested that applicants clarify the meaning of the claims.

9. Claims 11 (claim 12 dependent therefrom) and 17 (claim 18 dependent therefrom) are indefinite in the recitation of "conditions are those prevalent in a tissue of bodily fluid of an animal". The conditions that are "prevalent in a tissue of bodily fluid of an animal" are not defined by the specification or the claim and the scope of conditions encompassed by this term is indefinite. It is suggested that applicants replace the term with specific conditions that applicants consider "prevalent in a tissue of bodily fluid of an animal".

Claim Rejections - 35 USC § 112, First Paragraph

10. Upon reconsideration of the written description rejection of claims 1-3, 5-22, 24-30, and 41-44 under 35 U.S.C. 112, first paragraph, the rejection is withdrawn.

11. The enablement rejection of claims 1-30 and 41-44 under 35 U.S.C. 112, first paragraph, is maintained. The rejection was fully explained in a previous Office action. As stated in a previous Office action, the specification, while being enabling for a method for the preparation of a recombinant polypeptide by transforming a host cell with a nucleic acid encoding a recombinant protein consisting of the chymosin pro-peptide fused to a heterologous polypeptide, expressing the pro-peptide-heterologous polypeptide fusion protein, and adjusting the pH in order to activate the cleavage of the chymosin pro-peptide from the heterologous polypeptide or a chimeric nucleic acid sequence therefor and compositions thereof, does not reasonably provide enablement for a method of preparation of a recombinant polypeptide by transforming a host cell with a nucleic acid encoding *any* pro-peptide derived from an autocatalytically maturing zymogen (claim 1), *any* protease (claim 2), or *any* aspartic, serine or cysteine

protease (claim 3) upstream of a nucleic acid encoding a heterologous polypeptide, expressing the encoded fusion protein and altering the environment using *any* conditions (claim 1), or *any* pH, salt, or temperature conditions (claim 7) in order to cleave the pro-peptide from the recombinant polypeptide or a chimeric nucleic acid sequence encoding therefor and compositions thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Addressing A) to E) in Paper No. 17, applicants argue that: A) the determination of conditions for cleavage of a pro-peptide would be routine experimentation for one of skill in the art; B) the claims do not preclude non-specific cleavage of the recombinant polypeptide; C) applicants have provided examples of Sigma 2143 and Aspergillus saitoi acid protease with an ability to cleave the chymosin pro-peptide, thereby providing an example of a heterologous mature zymogen as set forth in claim 14; D) modification of a fusion protein comprising a pro-peptide derived from an autocatalytically maturing zymogen would be clear to one of skill in the art; and E) one of skill in the art could readily select a pro-peptide/heterologous polypeptide combination and develop the conditions necessary of cleavage. Applicants' arguments are not found persuasive. Applicants' arguments are not found persuasive.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s). The factors most relevant to this rejection are: the breadth of the claims, the quantity of experimentation necessary, the amount of direction or guidance presented, and the predictability or unpredictability of the art. As stated above, the claims are so broad as to encompass a method of preparation of a recombinant polypeptide by transforming a host cell with a nucleic acid encoding *any* pro-peptide derived from an autocatalytically maturing zymogen, *any* protease, or *any* aspartic, serine or cysteine protease upstream of a nucleic acid encoding a heterologous polypeptide,

expressing the encoded fusion protein and altering the environment using *any* conditions, or *any* pH, salt, or temperature conditions in order to cleave the pro-peptide from the recombinant polypeptide or a chimeric nucleic acid sequence encoding therefor and compositions thereof. The specification has not provided the guidance necessary for a method of preparation of a recombinant polypeptide by transforming a host cell with a nucleic acid encoding *any* pro-peptide derived from an autocatalytically maturing zymogen, *any* protease, or *any* aspartic, serine or cysteine protease upstream of a nucleic acid encoding a heterologous polypeptide, expressing the encoded fusion protein and altering the environment using *any* conditions, or *any* pH, salt, or temperature conditions in order to cleave the pro-peptide from the recombinant polypeptide or a chimeric nucleic acid sequence encoding therefor and compositions thereof as neither the specification nor the prior art has provided teachings as to the combination of *any* conditions that result in autocatalytic cleavage of *any* zymogen.

Furthermore, the term "pharmaceutical" in claim 41 implies a treatment of a disease. It is unpredictable what diseases can be effectively treated using a "pharmaceutical composition" comprising a chimeric nucleic acid sequence encoding a fusion protein, wherein the chimeric nucleic acid sequence comprises a nucleic acid encoding a pro-peptide derived from an autocatalytically maturing zymogen and a downstream nucleic acid encoding a heterologous polypeptide. Neither the specification nor the prior art provide sufficient guidance as to what specific diseases could be successfully treated by administering a "pharmaceutical composition" comprising said chimeric nucleic acid, and attempting to identify a disease treatable using such a "pharmaceutical composition" would constitute undue experimentation.

Also, although applicants have provided a two examples of heterologous proteases (Sigma 2143 and Aspergillus saitoi acid protease) that cleave the chymosin pro-peptide, it is unclear as to whether these proteases will cleave *any* pro-peptide of an autocatalytically maturing zymogen. Neither the specification nor the prior art provide sufficient guidance as to which combination of proteases and cleavable heterologous pro-peptides would obtain the desired biological effect. It is not routine in the art to screen for multiple proteases that cleave a heterologous pro-peptide as encompassed by claim 14 with a reasonable expectation of success in obtaining the desired biological effect.

Therefore, the expectation of obtaining a method of preparation of a recombinant polypeptide by transforming a host cell with a nucleic acid encoding *any* pro-peptide derived from an autocatalytically maturing zymogen, *any* protease, or *any* aspartic, serine or cysteine protease upstream of a nucleic acid encoding a heterologous polypeptide, expressing the encoded fusion protein and altering the environment using *any* conditions, or *any* pH, salt, or temperature conditions in order to cleave the pro-peptide from the recombinant polypeptide or a chimeric nucleic acid sequence encoding therefor and compositions thereof is highly unpredictable. Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102/103

12. Claims 1-7, 9-13, 15-26, 28-30, and 41-44 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Moloney (WO 96/21029). Claims 1-7, 9-13, 15-26, 28-30, and 41-44 are drawn to the methods for the preparation of a recombinant polypeptide by introducing into a host cell an expression vector comprising: a chimeric nucleic acid encoding a fusion protein comprising a nucleic acid encoding a pro-peptide from an autocatalytically maturing zymogen and a nucleic acid encoding a heterologous polypeptide immediately downstream of the nucleic acid encoding the pro-peptide as encompassed by claims 1-7, 9-13, and 15-19, a chimeric nucleic acid encoding a fusion protein comprising a nucleic acid encoding a pro-peptide from an autocatalytically maturing zymogen and a nucleic acid encoding a heterologous polypeptide immediately downstream of the nucleic acid encoding the pro-peptide, a vector comprising said chimeric nucleic acid, and host cells transformed therewith as encompassed by claims 20-30, and compositions comprising said chimeric nucleic acid as encompassed by claims 41-44.

Moloney teaches a method for expression and release of a recombinant polypeptide in a host cell by: a) introducing into a host cell a chimeric DNA sequence comprising: 1) a first DNA sequence capable

of regulating transcription in said host, 2) a second DNA sequence encoding a recombinant fusion polypeptide comprising a DNA sequence encoding a recombinant polypeptide and a DNA linker sequence encoding an amino acid sequence that is specifically cleavable by enzymatic or chemical means located between the sequences encoding an oleosin gene and a recombinant polypeptide and 3) a third DNA sequence encoding a termination region functional in the host; b) growing the host to produce the recombinant fusion polypeptide, (p 3, lines 14-26) and also teach that the peptide linker preferably includes a protease target motif (p 20, line 1). Moloney teaches a specific example of expression of an oleosin/hirudin gene fusion polypeptide. Moloney teaches that a hirudin gene fusion was prepared with the C-terminal end of an oleosin gene and that the gene sequences for oleosin and hirudin were separated by codons for an amino acid sequence encoding a Factor Xa endoprotease cleavage site and that huridin can be cleaved from the oleosin by the use of the Factor Xa cleavage site built into the fusion protein (p 46 and 47) and additionally teaches that the fusion protein can be an oleosin/chymosin fusion (p 52, lines 6-10). Moloney et al. teach that the recombinant polypeptide(s) to be produced as a fusion may include growth hormones (p 24, lines 19 and 20), the anticoagulant hirudin (p 25, lines 4 and 5), additives for animal feeds (p 24, line 17), for use in the food industry (p 24, line 27), proteins with a therapeutic or diagnostic value (p 25, lines 1-2) and teach that the recombinant protein "may be capable of undergoing self-release" and provide an example as follows: "the proteolytic enzyme chymosin undergoes self-activation from a precursor to an active protease by exposure of the precursor to low pH conditions. Expression of the chymosin precursor/oleosin fusion protein to conditions of low pH will activate the chymosin. If a chymosin recognition site is included between the oleosin and the chymosin protein sequences, the activated chymosin can then cleave the fusion proteins. This is an example of self release that can be controlled by manipulation of the conditions required for enzyme activity" (p 29, lines 3-10). Moloney also teaches "for uses where the fusion protein contains a peptide hormone that is released upon ingestion, the protease recognition motifs may be chosen to reflect the specificity of gut proteases to simplify the release of the peptide" (p 20, lines 7-10).

Applicants argue that Moloney does not anticipate the claimed invention because Moloney does not disclose a pro-sequence of an autocatalytically maturing zymogen that may be employed to facilitate cleavage of the pro-sequence from the heterologous polypeptide. This argument is not found persuasive. Moloney anticipates the use of an autocatalytically maturing zymogen to facilitate cleavage of the pro-sequence from the heterologous polypeptide (an oil body polypeptide), by disclosing that the recombinant fusion protein "may be capable of undergoing self-release" and provide an example as follows: "the proteolytic enzyme chymosin undergoes self-activation from a precursor to an active protease by exposure of the precursor to low pH conditions. Expression of the chymosin precursor/oleosin fusion protein to conditions of low pH will activate the chymosin. If a chymosin recognition site is included between the oleosin and the chymosin protein sequences, the activated chymosin can then cleave the fusion proteins. This is an example of self release that can be controlled by manipulation of the conditions required for enzyme activity" (p 29, lines 3-10).

Applicants further argue that the method of Moloney does not fall within the scope of the claimed invention, which specifies that the heterologous polypeptide must be *immediately* downstream of the pro-peptide. Applicants further argue that when the oil body protein is considered the heterologous polypeptide, the oil body protein can only be located either 1) upstream of the pro-peptide sequence or 2) downstream of the pro-peptide with the mature form of the chymosin separating the pro-peptide from the oil body polypeptide. Applicants' arguments are not found persuasive. Moloney teaches that the heterologous polypeptide (an oil body polypeptide), can be located either N- or C-terminally to a chymosin pro-peptide, corresponding to a nucleic acid encoding an oil body polypeptide with the pro-sequence located either upstream or downstream of the polynucleotide encoding the heterologous polypeptide (Figure 1 and caption, pages 9-10). Moloney teaches that "If a chymosin recognition site is included between the oleosin and the chymosin protein sequences, the activated chymosin can then cleave the fusion proteins" page 29, lines 7-9). Therefore, if the oil body polypeptide is downstream of the chymosin recognition site, the chymosin polypeptide sequence must not be *between* the oil body polypeptide and the chymosin recognition sequence, but is instead *upstream* of the chymosin recognition

sequence, i.e., as taught by Moloney, the order of the nucleic acids encoding the fusion polyptide would be a polynucleotide encoding a chymosin polypeptide, followed by a polynucleotide encoding a chymosin pro-peptide, followed by a polynucleotide encoding an oil body polypeptide. Therefore, Moloney anticipates or renders obvious claims 1-7, 9-13, 15, 19-26, 28-30, and 41-44 as written.

Claim Rejections - 35 USC § 103

13. Rejection of claim 8 is under 35 U.S.C. 103(a) as being unpatentable over Moloney (WO 96/21029) in view of McCaman et al. (J Biol Chem 261:15345-15348) is maintained. The rejection was fully explained in a previous Office action. Claim 8 is drawn to a method for the preparation of a recombinant polypeptide by altering the pH to a range of 2 to 4.5.

Applicants argue that because claim 8 is dependent upon claims rejected as being anticipated by Moloney, the reference of McCaman cannot teach or suggest the invention of claim 8. Applicants' argument is not found persuasive. As stated above, Moloney anticipates claim 7 from which claim 8 is dependent therefrom. Therefore, in view of the teachings of McCaman et al., claim 8 would have been obvious to one of ordinary skill in the art.

14. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Moloney (WO 96/21029) in view of Fine et al. (Gen Comp Endocrinol 89:51-61). Claim 27 is drawn to the nucleic acid sequences of SEQ ID NOs:1 and 3. Applicants disclose in the specification at page 4, lines 27-30 that SEQ ID NO:1 encodes a GST-chymosin pro-peptide-hirudin fusion protein and SEQ ID NO:3 encodes a polyhistidine-chymosin pro-peptide-carp growth hormone fusion protein.

Moloney discloses the teachings as described above. Moloney does not teach fusing either a GST or polyhistidine tag to his polypeptide. Moloney also does not teach a chymosin pro-peptide-carp growth hormone fusion protein.

Fine et al. teach the nucleic acid sequence of carp growth hormone (cGH) of expression of cGH in E. coli. Fine teach that administration of purified cGH to carp fed a low protein diet increased growth by 38 % relative to vehicle.

Also, one of skill in the art would have recognized the utility of fusing GST or polyhistidine to a polypeptide in order to facilitate purification by affinity chromatography as is well characterized and commonly used in the art.

Therefore, it would have been obvious to one of ordinary skill for a polynucleotide encoding a GST-chymosin pro-peptide-hirudin fusion protein because of the art-recognized use of GST and polyhistidine fusion tags and the teachings of Moloney and it would have been obvious to one of ordinary skill for polynucleotide encoding a polyhistidine-chymosin pro-peptide-carp growth hormone fusion protein because of the art-recognized use of GST and polyhistidine fusion tags and the teachings of Moloney and Fine et al. One would have been motivated to add a polynucleotide encoding a GST or polyhistidine fusion tag to the polynucleotide encoding the fusion polypeptide of Moloney et al. in order to facilitate purification of the expressed fusion polypeptide and one would have been motivated to add a polynucleotide encoding a GST or polyhistidine fusion tag and replace the polynucleotide encoding hirudin with a polynucleotide encoding cGH as taught by Fine et al. in order to facilitate purification of the expressed chymosin pro-peptide-cGH fusion polypeptide that is useful for increasing carp growth as described above. One would have a reasonable expectation of success for a polynucleotide encoding a GST-chymosin pro-peptide-hirudin fusion protein and a polynucleotide encoding a polyhistidine-chymosin pro-peptide-carp growth hormone fusion protein because of the results of Moloney and Fine et al. Therefore, claims drawn to the nucleic acid sequences of SEQ ID NOs:1 and 3, would have been obvious to one of ordinary skill in the art.

Conclusion

15. No claim is in condition for allowance. All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The examiner can normally be reached Monday-Friday from 8:00 am to 5:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Art Unit is (703) 308-4242. Any inquiry of a general nature or relating to

the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.

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